Type: Invited Presentation

Final Abstract Number: 36.001
Session: Tuberculosis: Hot Topics
Date: Saturday, April 5, 2014
Time: 15:45-17:45
Room: Room 1.40

Tuberculosis transmission oustide the home

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The history of tuberculosis has been viewed from the industrialised world perspective. TB incidence peaked in the mid-19th century and steadily decreased over the subsequent century. The current world distribution of TB shows that incidence is greatest in non-industrialised countries of sub-Saharan Africa and Asia. South Africa and Swaziland currently have the highest TB burdens in the world where more than 1% of their populations develop TB each year. Cape Town is one of the most heavily TB burdened cities in the world with more TB disease notified annually than the combined numbers of USA, Canada and UK. A comparison of South African and New York TB before chemotherapy demonstrates a 5- to 10-fold decline in TB in New York due to social and environmental factors, which did not occur in Cape Town. In addition to very high TB rates among people living with HIV, HIV-negative individuals living in Cape Town have similar TB burdens as reported a century ago. We therefore went on to explore and quantify the social and environmental locations and environmental factors maintaining the airborne transmission of TB within a local high TB burdened township.

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The interaction between antimicrobial and adjunctive therapies and the immune response to tuberculosis

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HIV-1 infected patients co-infected with some pathogens are at risk of developing of the immune reconstitution inflammatory syndrome (IRIS) when initiating antiretroviral therapy (ART). IRIS is characterized by inflammation leading to the clinical worsening of a treated infection or the unmasking of a previously undiagnosed condition or infection. It is commonly associated with tuberculosis (TB), 8-43% of the HIV-TB co-infected patients prescribed antitubercular treatment and ART develop TB-IRIS. Although IRIS has been recognised for over 20 years, relatively little was known until recently about its pathogenesis. Despite these advances in understanding IRIS, there remains no immune biomarker for diagnostic or prognostic purposes. This talk will review the risk factors associated with TB-IRIS, the challenges in studying this syndrome, and how T lymphocytes, dysregulated cytokine responses and innate immunity may contribute to the development of TB-IRIS.

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The role of vitamin D in tuberculosis pathogenesis and treatment

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Tuberculosis (TB) is a major cause of mortality, responsible for an estimated 1.4 million deaths worldwide in 2011. The global prevalence of latent *Mycobacterium tuberculosis* infection is estimated to be 32%, and this carries a 5–20% lifetime risk of reactivation disease. The emergence of drug-resistant organisms necessitates the development of new agents to enhance the response to antimicrobial therapy for active TB. Vitamin D was used to treat TB in the pre-antibiotic era, and its active metabolite, 1,25-dihydoxyvitamin D, has long been known to enhance the immune response to mycobacteria in vitro. Vitamin D deficiency is common in patients with active TB, and several clinical trials have evaluated the role of adjunctive vitamin D supplementation in its treatment. Results of these studies are conflicting, reflecting variation between studies in baseline vitamin D status of participants and dosing regimens. Vitamin D deficiency is also recognised to be highly prevalent among people with latent *M. tuberculosis* infection in both high- and low-burden settings, and observational epidemiological evidence links vitamin D deficiency with increased risk of both acquisition and reactivation of latent *M. tuberculosis* infection. Randomised controlled trials of vitamin D supplementation for the prevention of latent infection or active disease have yet to be performed, however. The conduct of such trials is a research priority, given the safety and low cost of vitamin D supplementation, and the significant public health consequences of positive results.

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New drugs for the treatment of tuberculosis

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Prior to the introduction of chemotherapy tuberculosis management relied upon aerotherapy, heliotherapy and good nutrition. Tuberculosis chemotherapy began in 1944 with the introduction

of streptomycin and para-amino-salicylic acid, later augmented by isoniazid. Between 1970-1980 rifampicin was introduced and with isoniazid and pyrazinamide made "short-course" 6-months treatment possible. The recent epidemic spread of HIV/AIDS and an increase in antituberculosis drug-resistance, making tuberculosis virtually untreatable in some instances, has placed tuberculosis programmes under severe pressure. New treatment regimens are direly needed.

For the first time in decades, there are now multiple new drugs in the pipeline for the treatment of tuberculosis. In addition, existing drugs are being repurposed or optimized with the goal of shortened treatment duration for drug-sensitive tuberculosis and safer, shorter treatments for multidrug-resistant tuberculosis. High-dose rifamycins and fluoroquinolones have treatment-shortening potential when used for drug-sensitive tuberculosis. Bedaquiline, an antituberculosis drug with a novel mechanism of action, and delamanid, a nitroimidazole, are entering phase 3 trials. Both improve rates of sputum culture conversion among patients with drug resistant tuberculosis. Other nitroimidazoles and oxazolidinones are in Phase 2 testing, as are combinations involving multiple new chemical entities.

Development of novel antituberculosis agents and regimens currently involves determination of early bactericial activity over the first 14 days of treatment as the first clinical investigation undertaken to establish a basic relationship between dose and antituberculosis activity and obtain limited information about safety and tolerability. The information obtained is refined in Phase 2 studies over 8-weeks that prepare the ground for definite Phase 3 studies for the conduct of which considerable capacity building and funding is still required.

A biomarker for early indication of treatment effects or cure could greatly simplify antituberculosis regimen development. Clear identification of the different populations of mycobacteria that are present in sputum at the start of treatment, and measurement of their rise or fall, could contribute to the identification of early signals of drug activity that provide sterilization of lesions. This area will start to be resolved only when the results of long-term studies of new regimens regarding relapse rates become available and candidate biomarkers can be validated.

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Antimicrobial stewardship: Limits for implementation

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Antibiotic stewardship programme (ASP) is a multifaceted approach to improve patients' clinical outcomes, prevent the emergence of antimicrobial resistance, and reduce hospital costs by prudent and focused antimicrobial use. Development of local treatment guidelines according to local ecology, rapid diagnostic in microbiology laboratory, dosage optimization following pharmacokinetic and pharmacodynamic profiles, formulary restriction for specific classes of antibiotics, appropriate duration of antibiotic treatment, ICU and wards specific antibiograms, programs of continuous education, feedback and prospective audit for healthcare workers, are fundamental components of an efficient ASP. Numerous studies have showed that it is possible to change antibiotic prescription attitudes in hospital, at different ecological, cultural and economical levels and ASP might play a significant role in the reduction of colonization and infections caused by antibiotic-resistant bacteria. Major risk in implementing ASP is the lack of consideration of local ecology and strict quality indicators. There is still an open debate over which outcomes to measure and the appropriate study design that can objectively assess ASP despite the limitations inherent in the structure of most such programs. European networks to define best strategies and antibiotic-care bundles need to be supported at national and international level.

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Social media for stewardship: Progress or a waste of time?

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Do you think the word "tweet" means the sound a bird makes? If a patient says "Doctor help me I'm addicted to twitter! and the doctor replies, "Sorry I don't follow you", are you laughing? If not, then this lecture will help you learn how to apply social media (Twitter and Facebook) in a meaningful way for antimicrobial stewardship programs (ASP). Health care providers who are expert Twitter-users state that Twitter is worth taking the time to figure out because of its powerful ability to amplify a message above and beyond current audiences. The world is losing the battle against antimicrobial resistant organisms. Antimicrobial stewards needs to engage colleagues, patients and consumers to understand that antibiotic resistance is one of the world's most pressing public health threats. Peer-reviewed articles in ID journals do not reach these audiences therefore additional strategies are necessary. Twitter for stewardship has a 2-fold purpose. First it can help advocate the stewardship message to preserve antibiotics. Secondly, twitter allows one to discover, interact and learn from other infectious diseases stewardship expert's worldwide. The twitter user must find a niche (stewardship) and then start to engage in trending topics (#antibioticresistance). The user can be passive on twitter and choose to follow organizations (@IDSAInfo @ECCMID @SouthAfricanASP @CDC_eHealth @WHO) or specific stewardship healthcare advocates (@IDPharmD) or the user can be become active and send out "tweets" that help advocate ASP. This is especially helpful for resource limited countries because twitter is free to use. Globally, there are over 1.1 billion people on Facebook. It allows the user to discover and interact with interesting people or organizations in the field of antimicrobial stewardship. This lecture will demonstrate how the CDC used Facebook to identify an outbreak in real-time and then connect with individuals to resolve the outbreak. The power behind social media and its impact on getting the antimicrobial stewardship message out to the world should